Statistical Analysis Plan

Study Code	**CBL-2016-01**
Study Title	**A Study to Evaluate the Performance and Safety of CBL-101 versus Vismed® Multi Eye Drops in the Management of Dry Eye**

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ART	Artificial Tears
ATC	Anatomical Therapeutic Classification
CFB	Change From Baseline
CI	Confidence Interval
D	Day
DD	Device Deficiency
DenDF	Denominator Degree of Freedom
DF	Degree of Freedom
eCRF	Electronic Case Report Form
ITT	Intent-To-Treat
max	Maximum
min	Minimum
mm	Millimeter
N	Number of observations
NA	Not applicable
NumDF	Numerator Degree of Freedom
OSD-QoL	Ocular Surface Disease-Quality of Life
pct	Percentage
PP	Per Protocol
Pr	Probability
PT	Preferred Term
Q	Question
Q1	First Quartile
Q3	Third Quartile
SD	Standard Deviation
SE	Standard Error
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time

2 INTRODUCTION

The purpose of this analysis plan is to outline the statistical methods to be implemented during the statistical analysis of the data from the study CBL-2016-01: "A Study to Evaluate the Performance and Safety of CBL-101 versus Vismed® Multi Eye Drops in the Management of Dry Eye".

This analysis plan is applied to the protocol version 5 dated 6th of June 2018. Results obtained from the analyses outlined in this document will be the basis of the final report for this protocol. As with any statistical analysis plan, the proposed methods and approaches to the data analysis should be flexible. Changes to this plan may arise if ongoing analysis of the data suggests deviations from the original plan, considering that these changes would provide a more reliable and valid analysis of the data. Therefore, any deviations which occur from this plan will be adequately documented.

3 STUDY OVERVIEW

3.1 Objectives

The primary objectives of this investigation are to show that the performance of CBL-101 Eye Drops is non-inferior to that of Vismed® Multi eye drops in subjects with moderate to severe keratoconjunctivitis sicca after 28 days, and to assess the safety of CBL-101 Eye Drops during a 90-day period with treatment administered 3 to 6 times per day.

3.2 Products

1. CBL-101 Eye Drops
2. Vismed® Multi Eye Drops

3.3 Study design

This is a multicenter, randomized, parallel group, investigator-masked, non-inferiority study to evaluate the performance and safety of CBL-101 Eye Drops in subjects with moderate to severe dry eye.

3.4 Study Endpoints

3.4.1 Primary Performance Endpoints

The primary performance endpoint for this study is mean change from baseline (CFB) in the study eye at Visit 4 (Day 28 ± 3 days) in ocular surface fluorescein staining score, combining corneal, nasal and temporal bulbar conjunctival fluorescein staining, each graded 0 to 5, according to the Oxford Scheme. The investigator will record the total score per eye (the maximum score is 15 [maximum of 5 for each of the 3 areas]).

The study eye will be the eligible eye with the highest total ocular surface fluorescein staining score at baseline or, if both eyes are eligible and have the same score, the study eye will be the right eye.

3.4.2 Secondary Performance Endpoints

The secondary performance endpoints include the following:

- Mean CFB in the study eye at Visits 3 and 5 in total ocular surface fluorescein staining score
- Mean CFB in the study eye in corneal fluorescein staining score at Visits 3, 4 and 5
- Mean CFB in the study eye in nasal conjunctival fluorescein staining score at Visits 3, 4 and 5
- Mean CFB in the study eye in temporal conjunctival fluorescein staining score at Visits 3, 4 and 5
- Mean CFB in the study eye in TFBUT at Visits 3, 4 and 5
- Evolution from baseline of Ocular Surface Disease-Quality of Life (OSD-QoL®) questionnaire scores at Visit 5 for all 7 dimensions: Daily Activities, Handicap and Work Difficulties, Giving up Make-up, Acknowledgement, Acceptance, Fear for the Future, Emotional Well-Being, and Global Question.
- Mean CFB in the global sum score of dry eye symptoms at Visits 4 and 5: sensation of dryness, foreign body, burning, stinging, itching, blurred vision, sensitivity to light, each graded from 0 to 4
- Mean CFB in the study eye in volume of tear fluid secretion as assessed by the unanaesthetized Schirmer test at Visit 4
- Frequency of investigational eye drop instillations, as reported in subject diary

3.4.3 Safety Endpoints

The safety endpoints include the following:

- Occurrence rates of ocular and non-ocular TEAEs.
- Visual Acuity measured with habitual correction, using Monoyer chart.

3.4.4 Tolerability and Ease-of-Use Endpoints

The tolerability endpoints are as follows:

- Assessment of investigational eye drop tolerability upon instillation as reported in subject diary (eye drop sensation and blurred vision)
- Assessment of ease-of-use of the bottle as reported in subject diary

3.5 Hypotheses

H0: ($\mu_{CBL\text{-}101\ Eye\ Drops} - \mu_{Vismed} \geq 2$)

versus

H1: ($\mu_{CBL\text{-}101\ Eye\ Drops} - \mu_{Vismed} < 2$)

Where μ = mean CFB in the study eye at Visit 4 (Day 28 ± 3 days) in total ocular surface staining score.

3.6 Sample size

Assuming a unilateral α risk of 2.5%, a β risk of 10% (90% power), a non-inferiority margin of 2 and a standard deviation of 2.5 on the primary endpoint, a sample size of 33 evaluable subjects per treatment group is necessary to demonstrate non-inferiority of CBL-101 Eye Drops to Vismed® Multi.

With a projected dropout rate of 10% and a protocol violation rate of 10%, a total of approximately 84 subjects with moderate to severe dry eye will be randomized in this clinical investigation.

3.7 Population

A total of up to approximately 84 subjects with a clinical diagnosis of moderate to severe keratoconjunctivitis sicca will be enrolled in this investigation. They will be randomized in a 1:1 ratio to receive either CBL-101 Eye Drops or Vismed® Multi.

Planned

Number of centres: 15 clinical sites

Number of countries: 1 (France)

Actual

Number of centres: 18 clinical sites (15 in France and 3 in Belgium)

Number of countries: 2 (France and Belgium)

3.8 Flow Chart

PROCEDURE/ASSESSMENTS	Visit 1 Screening ART run in Day -14 (up to -16 days)	Visit 2 Inclusion Baseline Day 0	Visit 3 Follow-up Day 7 (± 1 day)	Visit 4 Follow-up Day 28 (± 3 days)	Visit 5 Study Exit Day 90 (± 10 days)
Informed Consent	X				
Demographic data	X				
Current and relevant medical and ocular history	X				
Pregnancy test, if applicable	X				
Concomitant medication	X	X	X	X	X
Dry eye symptoms	X	X		X	X
OSD-QoL questionnaire		X			X
Visual acuity	X	X	X	X	X
Biomicroscopy	X	X	X	X	X
TFBUT	X	X	X	X	X
Fluorescein staining	X	X	X	X	X
Schirmer test		X		X	
Eligibility determination	X	X			
Randomization		X			
Dispense run-in ART	X				
Collect run-in ART		X			
Dispense diary	X (Diary A)	X (Diary B)		X (Diary C)	
Collect diary		X (Diary A)		X (Diary B)	X (Diary C)
Dispense investigational eye drops		X		X	
Collect investigational eye drops in a sealed container					X
Review subject diary for compliance		X	X	X	X
Adverse events	X	X	X	X	X
Exit subject					X

4 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

NA

5 POPULATIONS DEFINITIONS

Populations	
Population	**Definition**
Screened population	All screened patients
Intent-to-Treat Population (ITT)	All subjects who were randomized, who received at least 1 investigational eye drop instillation and have a baseline and at least 1 post-baseline assessment. The ITT population will be used to analyze all performance endpoints.
Per Protocol Population (PP)	All subjects from the ITT population who remained in the study through Visit 4 (Day 28) and who did not have any major protocol deviations*. The PP population will be used for the primary performance analysis and for secondary performance endpoints.
Safety Population	All subjects who received at least 1 dose of investigational eye drops
Safety ART Population	All subjects who received at least 1 dose of ART eye drops

Protocol deviations will include:

Code	Category
1	Non-compliance with consent procedure
2	Non-compliance with inclusion/Exclusion criteria
3	Non-compliance with study eye qualification
4	Non-compliance with visit schedule
5	Non-compliance with assessment procedure
6	Non-compliance with ART product dispensing
7	Non-compliance with ART product administration
8	Non-compliance with study product randomisation
9	Non-compliance with study product administration
10	Non-compliance with concomitant medication
11	Other* (to be defined if needed during the masked review)

Major protocol deviations (deviations with a significant impact on the primary endpoint) will be confirmed during the masked review.

6 ANALYSIS VARIABLES

6.1 Screening and baseline characteristics

Variables	Description
Demography	
Age	years
Gender	Male / Female
Patient questionnaire	
Contact lenses	Yes / No
Pregnant woman	Yes / No (If woman)
Breastfeeding woman	Yes / No (If woman)
Woman with no child-bearing potential (menopause or surgically sterile)	Yes / No (If woman)
Contraception	Yes / No (If woman of child-bearing potential)
Urine pregnancy test	Negative / Positive (if woman under contraception)
Participation in another study	Yes / No
Current and relevant medical and ophthalmic history	
Dry eye history	years
Dry eye etiology	Sjögren / Other (specify) / Unknown
Medical or surgical history	Yes / No
Relevant pathology	Yes / No
Medical ocular history description	- Description - Affected eye - Start date, End date / Ongoing
Medical non-ocular history description	- Description - Start date, End date / Ongoing
Severe ocular dryness accompanied by lid abnormality	Yes / No
Severe ocular dryness accompanied by corneal disease	Yes / No
Severe ocular dryness accompanied by ocular surface metaplasia	Yes / No
Severe ocular dryness accompanied by filamentary keratitis	Yes / No
Severe ocular dryness accompanied by corneal neovascularization	Yes / No
Ocular surgery, including laser surgery, in either eye within 180 days (6 months) prior to study start	Yes / No
History of ocular trauma, non-dry eye ocular inflammation, or ocular infection within 90 days prior to study start	Yes / No
History of ocular allergic disease or ocular herpes within 1 year prior to study start	Yes / No
History of any inflammatory ulcerative keratitis, recurrent corneal erosion, or uveitis	Yes / No

Variables	Description
Previous treatments	
Treatment taken during 3 months prior to this visit and stopped to date	Yes / No
Previous ocular treatment description	- Trade name - Dosage - Indication - Frequency - Dates of start and end - Route - Treated eye
Previous non-ocular treatment description	- Trade name - Dosage - Indication - Frequency - Dates of start and end - Route
Ocular therapy (either eye) with any ophthalmic medication, except tear substitutes, within 2 weeks prior to study start	Yes / No
Topical ocular steroidal or non-steroidal anti-inflammatory medication within 30 days prior to study start	Yes / No
Ocular therapy with immunosuppressants (eg, cyclosporine) within 90 days prior to study start	Yes / No
Occlusion therapy with lacrimal or punctum plugs within 90 days prior to study start	Yes / No
Concomitant treatments	
Patient under treatment(s)	Yes / No
Tear substitutes for at least 3 months prior to inclusion	Yes / No
If the patient is receiving a systemic treatment, is it stable (unchanged for 1 month or longer)?	Yes / No
Known hypersensitivity or contraindications to any of the ingredients in the test or comparator products or ART	Yes / No
Planned initiation of, or changes to, concomitant medication that could affect dry eye within 30 days of Visit 1 (Screening) or during the study	Yes / No
Expected to receive ocular therapy during the study	Yes / No
Expected to receive ocular therapy with immunosuppressants during the study	Yes / No

Variables	Description
Ophthalmic examinations at screening and baseline	
Global assessment of dry eye symptoms for both eyes: - Dryness sensation - Foreign body sensation - Burning sensation - Stinging sensation - Pruritus - Blurred vision - Sensitivity to light	(0) Absent (1) Mild and/or episodic; occurs under environmental stress (2) Moderate, episodic or chronic, stress or no stress (3) Severe, frequent or constant without stress (4) Severe and/or disabling and constant
Visual acuity (right and left eyes)	LogMAR = -Log(Visual acuity decimal)
Bio-microscopic examination on each eye: - Eyelid Margin Hyperemia - Eyelid Debris - Plugging of Meibomian Glands - Eyelid Erythema - Eyelid Swelling - Ocular Discharge - Conjunctival Chemosis - Conjunctival Hyperemia - Corneal Erosion - Corneal Edema - Corneal Infiltrates	(0) Absent (1) Mild (2) Moderate (3) Severe
Tear film break-up time (TFBUT) for each eye	Mean of the 3 values (in tenths of second)
Ocular surface fluorescein staining test on the 15-point Oxford scale for each eye	- Fluorescein staining score of the cornea (grades 0 to 5) - Fluorescein staining score of the temporal conjunctiva (grades 0 to 5) - Fluorescein staining score of the nasal conjunctiva (grades 0 to 5) - Global score (0 to 15)
Schirmer test without anesthesia in 5 minutes (D0 only) for each eye	Value in mm
Inclusion and exclusion criteria during screening	
Inclusion criteria	9 criteria (Yes/No)
Exclusion criteria	17 criteria (Yes/No)
Eligibility	Eligible / Ineligible
Screening number	
Inclusion and exclusion criteria at baseline D0	
Inclusion criteria	8 criteria (Yes/No)
Exclusion criteria	17 criteria (Yes/No)
Eligibility	Eligible / Ineligible
Randomisation number	
Studied eye	Right / Left

6.2 Performance Variables

Topic	Area	Analyzed parameters	Time of evaluation
Ocular surface fluorescein staining test	Studied eye	- Fluorescein staining score of the cornea (grades 0 to 5) - Fluorescein staining score of the temporal conjunctiva (grades 0 to 5) - Fluorescein staining score of the nasal conjunctiva (grades 0 to 5) - Global score (0 to 15)	D0 / D7 / D28 / D90
Tear film break-up time (TFBUT)	Studied eye	- Mean value in tenths of second	D0 / D7 / D28 / D90
Schirmer test without anesthesia in 5 minutes	Studied eye	- Value in mm	D0 / D28
Global assessment of dry eye symptoms	Both eyes globally	- Dryness sensation - Foreign body sensation - Burning sensation - Stinging sensation - Pruritus - Blurred vision - Sensitivity to light - Global Sum Score	D0 / D28 / D90
Ocular surface disease quality of life (OSD-QoL) questionnaire	-	Seven dimensions: - Daily activities - Difficulties with work and handicap - Giving up makeup - Acknowledgement of the disease - Acceptance of the disease - Fear for the future - Emotional well-being + 1 global question	D0 / D90

Methodology for OSD-QoL scores calculation

Dimension	Items	Maximum score
Daily activities	Q1 Q2 Q3 Q4 Q5	22
Handicap and Work Difficulties	Q6 Q7 Q8 Q9 Q10	22
Giving up Make-up	Q11	4
Acknowledgement of the disease	Q12 Q13	8
Acceptance of the disease	Q14	4
Fear for the future	Q15 Q16 Q17 Q18 Q19	20
Emotional Well-Being	Q20 Q21 Q22 Q23 Q24 Q25 Q26 Q27 Q28	27
Global Question	Q19	4

Each item is scored as stated in the questionnaire, a low score indicating a bad quality of life and high score a good quality of life.

For each dimension, a score will be computed as following

$$\text{Score} = \frac{\text{Sum of the items}}{\text{Max score for the dimension}} \text{ x } 100$$

In case of missing data or answer(s) « Not concerned », the score of the dimension will only be calculated if at least half of the items from the dimension are scored. The management of multiple answers will be described in the data entry guidelines and/or discussed during the masked review.

6.3 Safety Variables

Topic	Area	Analyzed parameters	Time of evaluation
Bio-microscopic examination	Each eye	- Eyelid Erythema - Eyelid Swelling - Ocular Discharge - Conjunctival Chemosis - Conjunctival Hyperemia - Corneal Erosion - Corneal Edema - Corneal Infiltrates	D0 / D7 / D28 / D90
Visual acuity test	Each eye	- LogMAR = -Log(Visual acuity decimal)	D0 / D7 / D28 / D90
Adverse events	All body	- At least one AE during the study - At least one TEAE during the study - At least one ADE during the study - At least one serious AE during the study - At least one serious TEAE during the study - At least one serious ADE during the study - At least one unanticipated serious ADE during the study - At least one anticipated serious ADE during the study	During all study
Adverse events	Ocular	- At least one ocular AE during the study - At least one ocular TEAE during the study - At least one ocular ADE during the study - At least one ocular TEAE related (possible, probable, certain) to the eye drops during the study - At least one ocular TEAE related (possible, probable, certain) to the procedure during the study - At least one serious ocular AE during the study - At least one serious ocular TEAE during the study - At least one serious ocular ADE during the study - At least one unanticipated serious ocular ADE during the study - At least one anticipated serious ocular ADE during the study - Ocular AE description	During all study

Topic	Area	Analyzed parameters	Time of evaluation
Adverse events	Non-ocular	- At least one non-ocular AE during the study - At least one non-ocular TEAE during the study - At least one non-ocular ADE during the study - At least one non-ocular TEAE related (possible, probable, certain) to the eye drops during the study - At least one non-ocular TEAE related (possible, probable, certain) to the procedure during the study - At least one serious non-ocular AE during the study - At least one serious non-ocular TEAE during the study - At least one serious non-ocular ADE during the study - At least one unanticipated serious non-ocular ADE during the study - At least one anticipated serious non-ocular ADE during the study - Non-ocular AE description	During all study
Device Deficiency (ART)	-	- At least one DD - DD description	Before D0
Device Deficiency (Investigational product)	-	- At least one DD - DD description	After D0

Safety parameters definitions

1) A TEAE (Treatment-Emergent AE) is defined as an AE that meets either of the following conditions:
   - Begins on or after the first instillation of investigational medical device on D0;
   - Begins before D0 and worsens in severity on or after the first instillation of investigational medical device on D0.

2) A DD (Device Deficiency) is an inadequacy of the investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
   It will be detected by any answer "YES" to the question "Has there been a deficiency of the medical device?".

3) An ADE (Adverse Device Effect) is an adverse event related to the use of an investigational medical device.
   It will be detected by any answer "YES" to the question "Has there been a deficiency of the medical device?" followed by an answer "YES" to the question "Has this led to an adverse event?".

6.4 Concomitant treatments

Topic	Area	Analyzed parameters	Time of evaluation
Concomitant treatments	Ocular	- Treatment description during the study	During all study
Concomitant treatments	Non-ocular	- Treatment description during the study	During all study
Change concomitant treatments	-	- Change in concomitant treatments Yes/No	D0 / D7 / D28 / D90

6.5 Compliance and exposure to treatment

Analyzed parameters	Description	Time of evaluation
Compliance evaluated by the investigator		
Diary returned by the patient	Yes / No	D0 / D28 / D90
After review of the subject's diary, has the patient compliance been good?	Yes / No	D0 (ART) / D7 / D28 / D90
Exposure and compliance to ART		
Exposure to ART	Number of ART days between the first ART instillation (date of the screening visit D-14) and the last ART instillation (as collected at D0 in the eCRF)	Between D-14 and D0
Average daily ART administration	Total number of ART administrations (as specified in the Diary A excluding the day of the visits Screening and D0) / Number of completed days in the Diary A excluding the day of the visits Screening and D0	Between D-14 and D0
% of days with at least one instillation	If the number of filled days ≥ 3/4 of the interval between D-14 and D0: 100 x Number of days with at least one ART instillation (Diary A) / Number of filled days in Diary A	Between D-14 and D0
Exposure and compliance to treatment		
Exposure to treatment	Number of treatment days between the first investigational drop instillation (date of baseline D0) and the last investigational drop instillation (as collected at the end of the study in the eCRF)	Between D0 and D90 or end of study
Average daily investigational drop administration	Total number of ART administrations (Diaries B+C excluding the day of the visits D0 and D90 or end of study) / Number of completed days in the Diaries B+C excluding the day of the visits D0 and D90 or end of study	Between D0 and D90 or end of study
Compliance at D28	If the number of filled days ≥ 3/4 of the interval between D0 and D28: 100 x Number of days with 3 to 6 treatment administrations (Diary B excluding the day of the visits D0 and D28 or end of study) / Number of filled days in the diary B (excluding the day of the visits D0 and D28 or end of study)	Between D0 and D28 or end of study
Global compliance	If the number of filled days ≥ 3/4 of the interval between D0 and D90/End of study: 100 x Number of days with 3 to 6 treatment administrations (Diaries B+C excluding the day of the visits D0 and D90 or end of study) / Number of filled days in the diary B+C (excluding the day of the visits D0 and D90 or end of study)	Between D0 and D90 or end of study

6.6 Tolerability and ease-of-use

Analyzed parameters	Description	Time of evaluation
Upon instillation, these eye drops are comfortable in my eyes	Strongly agree / agree / disagree / Strongly disagree	Diary D7 / D28 / D56 / End of last week or day before D90
Blurred vision sensation upon investigational eye drop instillation	Yes / No	Diary D7 / D28 / D56 / End of last week or day before D90
Duration of the blurred vision	0 minute (= No to "My vision is blurred") /]0 - 1] minute / [1 - 3] minutes / > 3 minutes	Diary D7 / D28 / D56 / End of last week or day before D90
The bottle is easy to use	Strongly agree / agree / disagree / Strongly disagree	Diary D28 / End of last week or day before D90

6.7 Other variables: Dates and Time intervals

Analyzed parameters	Description	Time of evaluation
Number of days between visits	Computed with the dates of visits	D0 / D7 / D28 / D90
Duration in the study	Computed with the dates of visits	D90 or End of study
Date of first visit	Computed with the dates of visits	D-14
Date of last visit	Computed with the dates of visits	D90 or End of study

6.8 End of study

Analyzed parameters	Description	Time of evaluation
Has the patient completed the study until D90?	Yes / No	End of study
Premature withdrawal: Screened patients (not randomised)		
Main reason for premature end of study	- Patient ineligible at visit D-14 - Patient ineligible at visit D0 - Other	End of study
Premature withdrawal: Randomised patients		
Last visit	D0/D7/D28/D90	End of study
Main reason for premature end of study	- Non compliance - Investigator's decision - Non-medical reason - Adverse event leading to study exit - Lost to follow-up - Consent withdrawn - Other	End of study

7 STATISTICAL ANALYSIS

7.1 Software documentation

Statistical analyses will be performed with SAS® version 9.4 or higher (SAS institute, North Carolina, USA).

7.2 General approach

Quantitative variables will be summarized into count of non-missing data, mean, standard deviation, minimum, maximum, median and, if necessary, 95% confidence interval of the mean.

Categorical data will be described into count and percentage with 95% confidence interval if necessary.

All statistical analyses will be performed at the 5% significance level using 2-sided test or 2-sided confidence intervals if necessary.

Normality will be tested by the Shapiro-Wilk at the 1% threshold.

7.3 Disposition of patients

The disposition of patients will be displayed on a flow-chart.

A table will present the number and percentage of patients by treatment group for each population and at each visit.

Reasons of exclusion from the study and protocol deviations (major and minor) will be described.

Study discontinuations and reasons will be listed.

7.4 Screening and baseline characteristics

Baseline characteristics will be described by treatment group on the ITT, PP and Safety populations.

For data collected on both eyes during the screening period, the description will be performed on the left and right eye separately (calculations unit = 1 eye).

For data collected on both eyes for randomised patients, the description will be performed on the study eye and fellow eye separately (calculations unit = 1 eye). As defined by the protocol; the study eye is the eligible eye with the highest total ocular surface fluorescein staining score at baseline or, if both eyes are eligible and have the same score, the study eye is the right eye.

Dry eye history as well as ocular and non-ocular history will be described in each group.

Visual acuity at baseline will be described by class for each treatment group: ≥ 8/10, <8/10 and ≥ 5/10, < 5/10 and ≥1/10, < 1/10.

Ocular prior treatments will be described in each group by defined therapeutic classes (third ATC level: S01A, S01B, S01C, S01E, S01F, S01G, S01H, S01J, S01K, S01L, S01X). The same descriptive analysis will be performed for non-ocular prior treatments (first ATC level: A, B, C, D, G, H, J, L, M, N, P, R, V).

All adverse events before investigational treatment administration will be described in each group by MedDRA'S « System Organ » and « Preferred Term ».

7.5 Primary performance endpoint analysis

The primary performance endpoint is the mean CFB in the study eye at visit 4 (D28 ± 3 days) in ocular surface fluorescein staining score, combining corneal, nasal and temporal bulbar conjunctival fluorescein staining score, each graded from 0 to 5, according to the Oxford scheme.

The primary performance endpoint analysis will be performed on the per-protocol population.

The primary performance endpoint will be analyzed by an analysis of covariance including the treatment as fixed effect and the baseline ocular surface staining score as covariate (SAS® Mixed procedure). The two-sided 95% confidence interval for the difference [CBL-101 Eye Drops: D28-D0] – [Vismed Multi: D28-D0] will be computed by the model. The non-inferiority will be demonstrated if the upper bound of the 95% CI is less than 2.

In addition to this model, and depending on the results of the baseline characteristics description, other relevant baseline covariates could be added to the model.

A sensitivity analysis including investigator site as covariate will also be performed using the same model.

Summary statistics for continuous variables will be presented for the total ocular surface fluorescein staining score at D0, D28, and for CFB at D28 for each treatment group.

This analysis will also be performed on patients from the ITT population. For subjects with missing values for the total ocular surface fluorescein staining score at D28, the last non-missing data will be used.

7.6 Secondary performance endpoint analyses

All secondary performance endpoint analyses will be performed on the ITT and PP populations. Results of statistical tests will be two-sided and given for information purpose only.

The secondary performance variables will be described by treatment group at each visit on raw values and on the changes / baseline D0.

The treatment groups will be compared at each post-baseline time using the same covariance model used to analyze the primary endpoint. Depending on their distribution, the multinomial data (such as the global assessment of dry symptoms evaluations) could be compared between groups using a generalized linear model for binomial or multinomial data (SAS® Glimmix Procedure) with the value at baseline as covariate.

7.7 Safety analyses

All safety analyses during the screening period will be performed on the Safety ART population.

All safety analyses for randomized subjects will be performed on the Safety population.

7.7.1 Bio-microscopic examination

Each sign will be described by treatment group and by eye (Studied eye and fellow eye) at each visit with an available data at the given visit.

Data at the follow-up visits will be cross-tabulated with the data at baseline D0 and will be described in 6 classes: No change (no sign) / Disappearance / Improvement / No change (persistence of the sign) / Aggravation / Onset. If necessary, modalities will be pooled depending on the number of subjects.

7.7.2 Visual acuity

The visual acuity will be described for each eye (Studied eye and fellow eye) by treatment group at D28 and D90 by class: ≥ 8/10, <8/10 and ≥ 5/10, < 5/10 and ≥1/10, < 1/10.

For changes / baseline, visual acuity decimal values will be transformed into LogMar values for summary statistics and compared between the 2 groups at D90 (Student t-test for independent samples or a Wilcoxon test if the data do not follow a normal distribution).

7.7.3 Adverse events

All adverse events variables, as described in the §3 "Safety variables" will be described and compared between groups (chi-square test or a Fisher exact test depending on the sample size).

All adverse events will be described in each treatment group by MedDRA's « System Organ » and « Preferred Term ».

All adverse events will also be listed by group.

7.8 Concomitant medication

All ocular concomitant treatments will be described in each treatment group by defined therapeutic classes (third ATC level: S01A, S01B, S01C, S01E, S01F, S01G, S01H, S01J, S01K, S01L, S01X). The same descriptive analysis will be performed for non-ocular concomitant treatments (first ATC level: A, B, C, D, G, H, J, L, M, N, P, R, V).

All concomitant treatments will also be listed by group.

7.9 Compliance and exposure to treatment

Results of statistical tests will be two-sided and given for information purpose only.

Listings of subjects compliance masked data will be provided for the masked review meeting to determine treatment compliance deviations.

7.9.1 ART exposure and compliance during screening period

Summary statistics for ART exposure analyses will be presented on the Safety ART population. ART exposure will also be compared between treatment groups (Student t-test for independent samples or a Wilcoxon test if the data do not follow a normal distribution).

ART compliance will include the average daily ART administration and the % of days with at least one instillation. Summary statistics for these data will be provided on subjects of the ITT and PP populations with an evaluable Diary A. They will also be compared between treatment groups in the PP population (Student t-test for independent samples or a Wilcoxon test if the data do not follow a normal distribution). Percentage of subjects with an average daily ART administration of <3, 3-6, >6 drops will also be provided.

The ART compliance evaluated by the investigator will also be described in both populations ITT and PP and be compared between treatment groups in the PP population (chi-square test or a Fisher exact test depending on the sample size).

7.9.2 Exposure and compliance during treatment period

The exposure to treatment will be described on the Safety population and compared between treatment groups (Student t-test for independent samples or a Wilcoxon test if the data do not follow a normal distribution).

Treatment compliance will include the average daily treatment administration, the number and % (compliance rate) of days with 3-6 treatment administrations at D28 and D90. These will be computed on subjects from the ITT and PP populations with evaluable Diaries B and C. Evaluable diary will be defined as Diary with at least ¾ treatment days filled by the patient. Treatment compliance will be described at D28 and D90 in ITT and PP populations and compared between treatment groups at D28 on the PP population only (Student t-test for independent samples or a Wilcoxon test if the data do not follow a normal distribution). Percentage of subjects with an average daily treatment administration will also be described by class (<3, [3-6], >6) and compared by treatment groups (chi-square test or a Fisher exact test depending on the sample size).

Subjects will be classified into 3 categories of compliance rate as follows:

1. Between ≥ 80% and 100% of compliance rate,
2. Between ≥ 60% and < 80% of compliance rate,
3. < 60% of compliance rate.

This variable will be described and compared by treatment groups (chi-square test or a Fisher exact test depending on the sample size).

The compliance evaluated by the investigator will also be described at each visit and compared by treatment groups (chi-square test or a Fisher exact test depending on the sample size).

All compliance analyses will be performed on the ITT and PP populations.

7.10 Tolerability and ease-of-use

These analyses will be performed on the Safety population. Results of statistical tests will be two-sided and given for information purpose only.

Each variable will be described by group at each evaluation time. Both groups will be compared at D90 by a chi-square test or a Fisher exact test depending on the sample size.

7.11 Other analyses

The time intervals between the baseline (D0) and each post-baseline visit, between D0 and the last visit and between D0 and the end of treatment will be calculated and described by groups. The dates of first visit of first subject and last visit of last subject will be provided.

7.12 Missing data

For subjects who discontinued the study early, analyses of change from baseline to endpoint for continuous variables will be based on the last non-missing post-baseline data (last observation carried forward data imputation methodology).

For safety data, if the causality assessment of an AE is missing, it will be imputed as “Probably” related to the investigational treatment. Likewise, if the severity is missing, the AE will be assessed as “Severe”.

Regarding diaries, missing data will be discussed during the masked review.

7.13 Tables and listings examples

7.13.1 Global appearance

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7.13.2 Summary statistics

7.13.2.1 Quantitative data

TITLE				
		Treatment		
Parameter	Statistic	CBL-101 Eye Drops	Vismed Multi	Total
Analyzed variable	*N*			
	Mean (+/-SD)			
	Min ; Max			
	Median			
	Q1 ; Q3			
	95% CI			

7.13.2.2 Qualitative data

TITLE				
		Treatment		
Parameter		CBL-101 Eye Drops	Vismed Multi	Total
Analyzed variable	*Modality 1*	n (pct)	n (pct)	n (pct)
	Modality 2	n (pct)	n (pct)	n (pct)
	…	n (pct)	n (pct)	n (pct)
	Total	n (pct)	n (pct)	n (pct)

7.13.3 Performance endpoints analyses

7.13.3.1 Quantitative data (including primary endpoint)

- Global effects

Analyzed variable Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Group				
Value at baseline				
Other covariable				

- Model estimates

Analyzed variable					
CBL-101 Eye Drops LSMeans		**Vismed Multi LSMeans**		**CBL-101 Eye Drops – Vismed Multi Difference of LSMeans**	
Estimate (+/-SE)	**95% CI**	**Estimate (+/-SE)**	**95% CI**	**Estimate (+/-SE)**	**95% CI**

7.13.3.2 Qualitative data

- Global effects

Analyzed variable Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Group				
Value at baseline				
Other covariable				

- Model estimates

Analyzed variable		
	Odds ratio	
Comparison	**Odds Ratio**	**95% CI**
CBL-101 Eye Drops / Vismed Multi		

7.13.4 Adverse events table

System-Organ	Preferred Term	CBL-101 Eye Drops		Vismed Multi		Total	
		n	% / N patients	n	% / N patients	n	% / N patients
System-Organ 1	PT 1						
	PT 2						
	PT x						
	TOTAL						
System-Organ 2	PT 1						
	PT 2						
	PT x						
	TOTAL						
System-Organ x	PT 1						
	PT 2						
	PT x						
	TOTAL						

n = Number of patients with a least the AE once.
N = Total number of patients

7.13.5 Concomitant treatments table

Therapeutic class	CBL-101 Eye Drops		Vismed Multi		Total	
	n	% / N patients	n	% / N patients	n	% / N patients
Therapeutic class 1						
Therapeutic class 2						
Therapeutic class X						

n = Number of patients with a least the treatment once.
N = Total number of patients

7.13.6 Patients data listings

Provided in annex.